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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/665,374	09/16/2003	Se-Jin Lee	JHU1800-3	5508

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/665,374	LEE ET AL.	
	Examiner	Art Unit	
	Iqbal H. Chowdhury, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/16/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

In response to a previous Office action, a non-final requirement (mailed on October 13, 2006), Applicants filed an amendment on January 16, 2007 amending claims 1, 3, 5 and canceling claims 4,and 16-66 is acknowledged. Claims 1-3 and 5-15 are pending and under consideration in the instant Office action.

Applicants' arguments filed on January 16, 2007, have been fully considered but are not deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Maintained - Claim Rejections - 35 U.S.C. § 112

Previous rejection of claims 1-3 and 5-15 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained. This rejection has been described in length in previous Office Action. Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons.

These claims are directed to a method of modulating any myostatin protein activation, comprising contacting any latent myostatin complex comprising any myostatin pro-peptide and any myostatin C-terminal fragment, and a metalloprotease, wherein the metalloprotease is bone morphogenic protein-1/tolloid (BMP-1/TLD) family member that can cleave the myostatin pro-peptide, with an agent that increases or decreases proteolytic cleavage of the pro-peptide by said metalloprotease, thereby modulating myostatin activation.

Applicants argue that the function of myostatin is "common knowledge" or was well known in the art at the time of the filing of the present application and applicants were the first to describe myostatin or GDF-8 function as a "negative regulator of skeletal muscle mass. Applicants also argue that myostatin is "highly conserved" across many species, suggesting conservation of myostatin function, "conserved C-terminal region" is the region following the RXXR proteolytic processing site and "C-terminal fragment", or its equivalent, the "C-terminal region", results in a polypeptide fragment that is about 109 amino acids in length, which is the mature active form of myostatin, formed upon removal of the N-terminal prodomain by proteolytic cleavage. Applicants further argue that the initial discovery of GDF-8/myostatin structure and function of the present invention is disclosed by the applicant. Thus, it was "common knowledge" and well known in the art at the time of the filing of the present application that the claimed "myostatin activation" refers to myostatin function as a negative regulation of skeletal muscle mass/growth. Furthermore, applicants submit that the skilled artisan would clearly understand "a myostatin C-terminal fragment" to be the C-terminal fragment generated upon the proteolytic cleavage of full-length myostatin at the RXXR processing site.

With regard to "a metalloprotease" applicants argue that the skilled artisan would not interpret "a metalloprotease" to be "any" protease and Example 1 clearly describes that the BMP-1/TLD metalloproteases (e.g., BMP-1, mTLD, mTLL-1 and mTLL-2) can cleave the pro-peptide in purified form or in a complex with the myostatin C-terminal dimer (i.e. a "latent myostatin complex"). Therefore, based on the foregoing, Applicants submit, that based on the "facts", the terms/phrases recited in the claims are consistent with the "plain meaning" and/or are

described/defined in the specification such that "a person skilled in the art would recognize applicant's disclosure a description of the invention defined by the claims". MPEP §2163.04.

Applicant's arguments and Exhibits have been fully considered but are not deemed to be persuasive to overcome the rejection on Written description issues. As mentioned in the previous Office Actions, claims 1-3 and 5-15 are directed to a method of modulating any myostatin protein activation, comprising contacting any latent myostatin complex comprising any myostatin pro-peptide and any myostatin C-terminal fragment, and a metalloprotease, wherein the metalloprotease is bone morphogenic protein-1/tolloid (BMP/TLD) family member that can cleave the myostatin pro-peptide, with an agent that increases or decreases proteolytic cleavage of the pro-peptide by said metalloprotease, thereby modulating myostatin activation. The specification teaches the structure of only several representative species of such agents, which modulate myostatin activation, and single representative species of myostatin and metalloprotease. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than function of said agent, which inhibits cleavage of latent myostatin and functionality of myostatin and metalloprotease. Claims (currently submitted) still read on any agent or any myostatin or any metalloprotease used in the method to modulate myostatin activation. Claims do not give any structural feature of said agents used in the method, which is required for fulfilling Written description requirements. As discussed in the written description guidelines the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional

characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species, which are adequately described are representative of the entire genus. **Thus, when there is substantial variation within the genus, one must describe a sufficient structure and variety of species to reflect the representative structure variation within the genus.** Satisfactory disclosure of a representative structure and number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of species disclosed. For inventions in an unpredictable art, adequate written description of a genus cannot be achieved by disclosing the structure of small portion of only one species within the genus. The genus of agents having inhibitory function of myostatin activation is structurally diverse as it broadly encompasses many mutants and variants comprising said functions having different structures. As such, the disclosure solely of functional features coupled with minor structural feature that may or may not present in all members of the genus is insufficient to be representative of the attributes and features of the entire genus. Therefore, the rejection is maintained.

Previous rejection of claims 1-3 and 5-15 under 35 U.S.C. 112, first paragraph, on Enablement issues is maintained. This rejection has been described in length in previous Office Action. Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicants argue that the present application clearly describes how to make and use the claimed invention and is not undue or unreasonable, wherein Example 1 describes that the BMP-

1/TLD metalloproteases (e.g., BMP-1, mTLD, mTLL-1 and mTLL-2) can cleave the pro-peptide in purified form or in a complex with the myostatin C-terminal dimer (i.e. a "latent myostatin complex") and Example 2 describes that using a luciferase activity assay, "a comparison of the amount of myostatin activity present in the mTLL-1-treated sample and the degree of proteolytic processing of the pro peptide by mTLL-1 in this sample revealed that at least about 50% of the proteolytically-cleaved myostatin complex was active in the reporter assay and Example 3 describes a series of peptides based on myostatin pro-peptide sequence and retaining the "RD" BMP-1/TLD cleavage site: wild-type peptides (SEQ ID NO:9, 12, 15, 18 and 21); mutant peptides whereby arginine residue has been mutated to a glutamine residue (SEQ ID NO:10, 13, 16, 19 and 22); and mutant peptides whereby aspartic residue has been mutated to an alanine residue (SEQ ID NOs: 11, 14, 17, 20 and 23). Further, in vivo studies demonstrate that the same mutant pro-peptide/Fc fusion protein effectively resulted in an animal with increased muscle mass, which is indicative of activation of the latent myostatin complex. Thus, the skilled artisan can make and use "any myostatin pro-peptide" provided the pro-peptide contains the "RD" BMP-1/TLD cleavage site; "any myostatin C-terminal fragment" containing the RXXR processing site; "any metalloprotease" so long as it recognizes the "RD" cleavage site in the myostatin pro-peptide; and "any agent that increases or decreases proteolytic cleavage of the pro-peptide" can be explored. Therefore, the skilled artisan needs only to look to Applicants disclosure to make and use the claimed invention.

As mentioned in the previous Office Actions, claims, while being enabling for a method of modulating activation of myostatin protein of SEQ ID NO: 2 by a metalloprotease of human

BMP-1 that can cleave the myostatin pro-peptide, with peptide agents such as SEQ ID NO: 9-23 that decreases proteolytic cleavage of the pro-peptide by the metalloprotease BMP-1, thereby decrease myostatin activation, doe not reasonably provide enablement for a method of modulating any myostatin protein activation, comprising contacting any latent myostatin complex comprising any myostatin pro-peptide and any myostatin C-terminal fragment, by using any metalloprotease that can cleave the myostatin pro-peptide, with any agent that increases or decreases proteolytic cleavage of the pro-peptide by the metalloprotease, thereby modulating myostatin activation.

Claims are so broad as to encompass a method of modulating any myostatin activation (any metalloprotease specific) by using any agent that increases or decreases proteolytic cleavage of the pro-peptide, thereby modulating any myostatin activation. The scope of the claims is very broad comprising extremely large numbers of proteins, peptides or chemicals broadly encompassed by the claimed "agents". The claims read on anything as an agent without any structural limitations i.e. claims do not provide any structural feature of said agents used in the method. However, in this case the disclosure is limited to the amino acid sequences of only a few peptides agents and a single representative myostatin protein.

Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function and physicochemical properties.

For example, Branden et al. (1991) teach that (1) protein engineers are frequently surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules of protein stability, and (3) the difficulties in designing de novo stable proteins with specific functions. The teachings of Branden et al. are further supported by the teachings of Witkowski et al. (1999) and Seffernick et al. (2001), where it is shown that even small amino acid changes result in enzymatic activity changes i.e. each of the myostatin and metalloprotease proteins from different genus or species are different even within the genus or species are different and may exhibit different functions, and physicochemical properties. However, in the instant case the disclosure is limited to the several species of agents (peptides), single representative species of myostatin and metalloprotease. The specification clearly requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of agents have the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute **undue** experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification. As previously stated the applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a method of modulating any myostatin activation (any metalloprotease

specific) by using any agent that increases or decreases proteolytic cleavage of the pro-peptide, thereby modulating myostatin activation. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of any peptide agent that modulates metalloprotease-mediated activation of latent myostatin having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). Therefore, the rejection is maintained.

Maintained-Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Previous rejection of Claims 1-3 and 5-15 under 35 U.S.C. 102(e) as being anticipated by Lee et al. (US PGPUB 2002/0157126 A1, publication 10/24/2002, filing date 4/24/2001, claim priority of 60/054,461 of 8/1/1997) is maintained. This rejection has been described in length in previous Office Action. Applicant's arguments have been fully considered but are not deemed to be persuasive to overcome the rejection. Instant claims are directed to a method of modulating any myostatin protein activation, comprising contacting any latent myostatin complex comprising any myostatin pro-peptide and any myostatin C-terminal fragment, and a metalloprotease, wherein the metalloprotease is bone morphogenic protein-1/tolloid (BMP-1/TLD) family member that can cleave the myostatin pro-peptide, with an agent that increases or

decreases proteolytic cleavage of the pro-peptide by said metalloprotease, thereby modulating myostatin activation.

Applicants argue that to anticipate, a single reference must inherently or expressly teach each and every element of claimed invention and the reference must be enabling to place the allegedly disclosed matter in the possession of the public. Applicants further argue that the claimed invention must be distinct from what is apparently inherent in the reference, Applicants also argue that Lee cannot anticipate the claimed invention because Lee, does not disclose each and every element of the claimed invention and Lee must be enabling thus placing the allegedly disclosed matter in possession of the public. Applicants further argue that Lee, does not describe any metalloproteases, and absent any description of a metalloprotease, the skilled artisan would not be put "in possession" of the alleged disclosed matter and cannot make the claimed invention "without further experimentation". Furthermore, applicants state that Lee only suggests (i.e. "may") that a latent myostatin complex exists based on a latent complex existing for TGF-beta and it's pro-peptide. Therefore, because Lee does not disclose each and every element, Lee cannot anticipate the claimed invention.

This is not found persuasive because Lee et al. indeed disclose a method of modulating a myostatin activation, comprising contacting a latent myostatin complex comprising a myostatin pro-peptide and a myostatin C-terminal fragment and BMP that can cleave the myostatin pro-peptide into prodomain i.e. N-terminal fragment and mature myostatin i.e. C-terminal fragment, with an agent (peptides) that decreases proteolytic cleavage of the pro-peptide by the BMP, thereby modulating myostatin activation. While applicants assert that Lee et al. do not teach metalloprotease, Lee et al. indeed teach BMP (see p3, Col 2, paragraph 2, line 19), a

metalloprotease of BMP family. Lee et al. further teach a method of increasing myostatin activation. Lee et al. furthermore teach the method, which comprise in vitro and in vivo methods of myostatin activation. Lee et al. also teach administering the agent to a subject wherein the agent decrease proteolytic cleavage of the propeptide by the metalloprotease, thereby increase muscle mass and decrease fat content in said subject, wherein the subject an animal raised as a food source, such as avian or piscine species or ovine, porcine or bovine species or chicken or turkey or a human subject. According to MPEP: A reference contains an "enabling disclosure" if the public was in possession of the claimed invention before the date of invention. "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." (see In re Donohue, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985). Lee et al. is an enabling reference because Lee et al. indeed teach a method of modulating (more specifically inhibition) myostatin activation by inhibiting pro-myostatin cleavage by an agent that affects myostatin signal transduction. In addition, Lee et al. teach peptide, which can be made by peptide synthesizer, as well as gene encoding pro-myostatin, BMP, a metalloprotease and how to cleave pro-myostatin and how to inhibit including assay method. In addition, Lee et al. teach administering said peptide into animal, i.e. Lee et al. teach every claimed element and how to make pro-myostatin, myostatin, assay method of cleavage, use of inhibitor or agent, which inhibit cleavage as well as how to use.

Therefore, Lee et al. anticipates claims 1-3 and 5-15 of the instant application and the rejection is maintained.

Conclusion

Claims 1-3 and 5-15 are rejected.

Applicants must respond to the objections/rejections in each of the sections in this Office action to be fully responsive in prosecution. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P., 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R., 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R., 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury, Ph.D. whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 703-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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